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Blood coagulation and fibrinolysis of the newborn viewed as perinatal factors

I. Blood coagulation and fibrinolysis of the newborn viewed as obstetrical factors

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1 Introduction

"Hemorrhage" in the newborn is a major problem in the adaptation to extrauterine life and has been recognized for some time as merely a result of Vitamin K deficiency. It is also known that fibrinolysis, especially the balance between the plasminogen-activator and plasmin inhibitor, plays an important role in this disease during the neonatal period.

DIC (disseminated intravascular coagulation), often seen in the pathological newborn infant, has recently been proven as one of the important factors of the respiratory distress syndrome (RDS) [1, 2, 4, 6, 16]. On the other hand, any imbalance of the acid-base physiology in neonatal asphyxia is a crucial factor in determining whether or not the newborn will survive. With this in mind, attempts were made to correlate these factors throughout the neonatal period. There are two important points in this problem. The first is the relationship between the asphyxia in the newborn and DIC, and the second is the respiratory distress syndrome occuring after birth.

In order to adapt to extrauterine life, it is necessary for newborn infants to maintain a certain balance in their blood coagulation and fibrinolysis.

From this point of view, an investigation of the blood coagulation-fibrinolytic system was performed in the cord-venous blood of cases of asphyxia in relation to various forms of delivery (breech presentation, preeclampsia, cord around the neck, delayed delivery) and respiratory distress syndrome.

2 Material and methods

2.1 Material

The subjects in the present investigation are 102 newborn infants delivered in the Departments of Obstetrics at Hokkaido University Hospital, and at the Free University, Berlin. These may be divided into 30 normal deliveries, 23 delayed deliveries, 21 preeclampsia, 18 breech presentations, 10 cases of nuchal cord or prolapse of the cord.

2.1.2 Method of research

After delivery, prior to the first breath, a 20 cm section of the umbilical cord was clamped and blood samples were taken from the cord vein, using a disposable syringe. Actual pH values were measured by Astrup micro gasanalysis.

2.2 Blood coagulation parameters

To test for the blood coagulation and the fibrinolytic system, the following parameters were determined.

2.2.1 Thrombelastogram (TEG)

This apparatus is useful in describing the outline of the process of blood coagulation and fibrinolysis. The advantage is that only 0.36 ml of blood is required and the procedure is relatively simple. The thrombelastograph is described as follows using Fig. 1 as a reference [3].

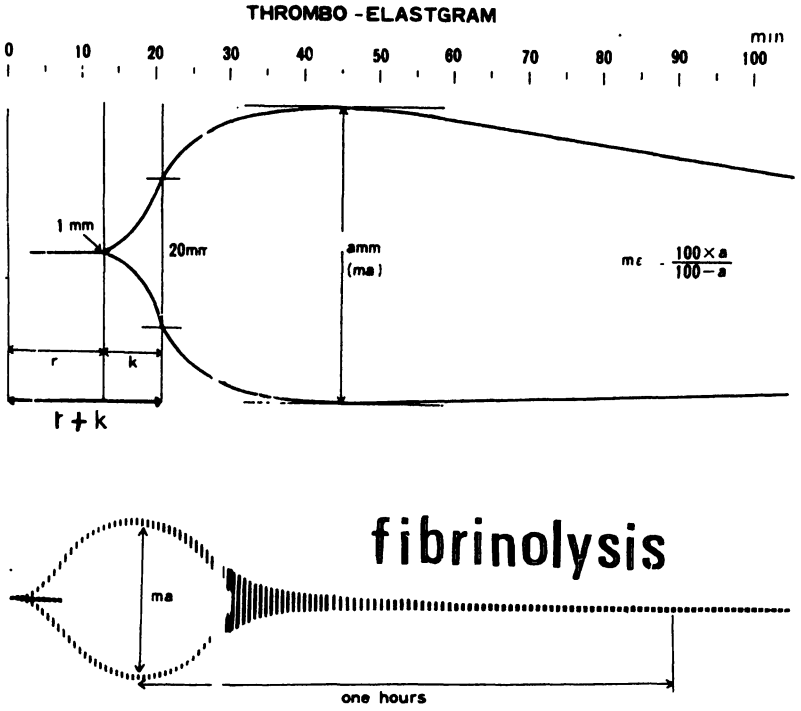

Fig. 1. Each parameters of the thrombelastogram and typical fibrinolysis.

r: time required from blood sampling until the time when the amplitude reaches 1 mm, this is equal to the time required for thromboplastin formation.
k: time required for the amplitude to reach 20 mm from 1 mm, which represents the time required for thrombin formation.
ma: maximum amplitude, which is related to the number of platelets and the amount of fibrinogen.

Depicting the occurrence of fibrinolysis frequently presents problems, i.e. when a straight line reappears following the development of a maximum amplitude (ma) (Fig. 1).

2.2.2 FDP (fibrin degenerative product)

The split products can be detected by various methods such as immune precipitation, turbidimetry, gel diffusion, immune electrophoresis, latex test and tanned red cell hemagglutination inhibition immune assay (TRCHII, Teikoku-hormone, Tokyo, Japan).

a) The antiserum was dissolved in 0.5 ml of phosphate buffer.
b) The red cells were suspended in 1.0 ml of phosphate buffer.
c) Test serum (0.1 ml), antiserum (0.1 ml) and red cells suspension (0.2 ml) were pipetted into a test tube.

When the test solution contains antigen (fibrinogen, split products from fibrinogenolysis or fibrinolysis) no agglutination of the red cells occurs, thus leading to a ring formation at the bottom of the test tube (Fig. 2) [17]. In order to avoid early formation of FDP in vitro, a fibrinolysis inhibitor solution such as Trasylol (BAYER, Leverkusen, West-Germany) was added immediately after collecting the blood samples prior to any further analysis.

2.2.3 Euglobulin lysis time

Euglobulin lysis time was recorded by an automatic clot lysis time recorder (KANAMAN, London, Great-Britain).

2.2.4 Normotest

Normotest is a standardized lyophilized reagent which has been devised for detection and control of changes in the coagulation factors (prothrombin), VII (proconvertin) and X (STUART–PROWER-

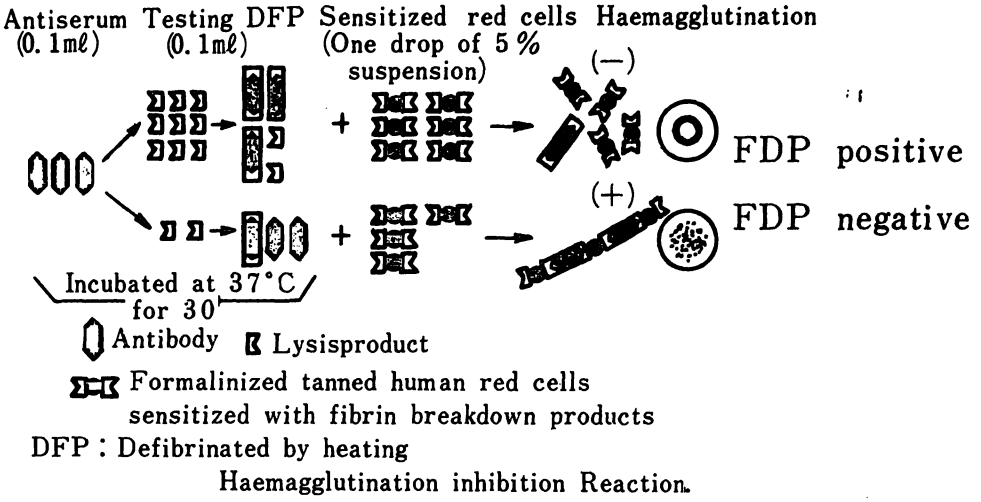

Fig. 2. The determination of FDP (Fibrin splits product) by the method of tanned red cell hemagglutination inhibition immune assay [11].

factor). Blood samples (0.02 ml) were obtained from the umbilical cord or from the heal using Sahli's melangeur; the blood were mixed immediately with 0.5 ml of Normotest sample in a test tube.
The clotting time was recorded and the Normotest value was obtained from the standard curve.

2.2.5 Factor V and factor VII

Both factors were tested with the reagents produced by DADE.

2.2.6 Fibrinogen (RATNOFF–MENZIE) [18]

2.3 Determination of estriol

The E_3 kit (Teikoku-hormone, Tokyo, Japan) was used prior to delivery (especially in delayed delivery and preeclampsia cases).
Urinary estriol was measured and used as a functional criterion of the placenta. Less than 10 mg/day was the low value group (6 cases), 10–20 mg/day was the slightly lowered group (18 cases), and 20–50 mg/day was set as the normal group (21 cases) (Tab. I).

Tab. I. Classification of the newborn infants by the urinary estriol excreted from their mothers.

10 mg/day	===== low value group
10---20 mg/day	===== slightly lowered group
20---50 mg/day	===== normal group

The relationship between the normotest and estriol levels in urine was studied.

Statistical evaluation

Distribution of the data was evaluated by use of mean values and standard deviation, student t-test and the u-test for paired observation was utilized to compare the data from moribund cases (part I) or RDS cases (part II) with those from normal babies (part I) and SFD without complications (part II).

3 Results

The respective results of the actual pH, base excess, Pco_2 of cord venous blood are shown in Tab. II and Tab. III (2.1.2). In 4 cases of death from the 102 investigated, actual pH value exhibited an anverage of 6.92, which is far below the lower limit of 7.10 for fetal distress. Moreover, from the lowering of fibrinogen which in turn raises FDP, intravascular coagulation might be assumed.
The value of r, r + k and ma of the thrombelastogram (2.2.1) are shown in Tab. IV. The TEG of the newborn infant is characterized by the following points.

a) r and r + k are shorter than in normal adults.
b) ma is wider than in normal adults.

This indicates that the normal newborn infant has an in vitro tendency to hypercoagulability.

Tab. II. Microgasanalysis of cord venous blood (mean ± S.D)

Actual pH	normal delivery (30)	7.27 ± 0.08
	delayed delivery (23)	7.21 ± 0.07
	Preeclampsia (21)	7.22 ± 1.14
	breech presentation (18)	7.11 ± 0.18
	cord nuchal or prolapse (10)	7.15 ± 0.11
Base Excess	normal delivery (30)	− 7.8 ± 1.41
	delayed delivery (23)	− 9.2 ± 2.36
	preeclampsia (21)	− 8.3 ± 1.63
	breech presentation (18)	−12.5 ± 2.43
	cord nuchal or prolapse (10)	−10.3 ± 1.25
PO_2	normal delivery (30)	24.5 ± 3.10
	delayed delivery (23)	17.0 ± 3.61
	preeclampsia (21)	16.8 ± 2.90
	breech presentation (18)	10.8 ± 6.10
	cord nuchal or prolapse (10)	12.5 ± 5.83
PCO_2	normal delivery (30)	45.0 ± 9.8
	delayed delivery (23)	55.1 ± 10.6
	preeclampsia (21)	56.5 ± 18.7
	breech presentation (18)	58.8 ± 14.4
	cord nuchal or prolapse (10)	56.4 ± 9.7

On the other hand, in the cases of acidosis mentioned above, the ma-value of the TEG was narrower than 25 mm, whereas the value of r and r + k showed no particular relationship with the actual pH (Tab. V).

The values of FDP are shown in Tab. V (2.2.2).

In the moribund cases with a pH value of less than 7.1, the value of FDP was significantly higher than in those with a pH value of over 7.1.

Euglobulin lysis time (2.2.3) of newborn infants is shorter than that of normal adults. No correlation could be found, however, between the euglobulin lysis time and these obstetric factors (Fig. 3).

Normotest, (2.2.4) factor V and factor VII (2.2.5)

The fluctuation in the results under the aspect of the age in days were studied in three groups with different placental function according to their estriol values: a low value group, a slightly lowered group and a normal group. The normotest of normal infants did not approach the value of normal adults until 6–7 days after birth.

In contrast, the babies of the low value group showed a slow rise as late as a week after birth, whereas no significant difference between the slightly lowered group and the normal group was detected (Fig. 4). Although this low value group may not be considered as premature, it may be said that the negative influence on the fetus is remarkable, particularly as to the insufficiency and frailty of the fetal liver and placental function.

It is furthermore remarkable that the values of factor V and VII in delayed delivery are lowered (Tab. VI).

Tab. III. The results of microgasanalysis and blood coagulation factors of newborn infants who died immediately after birth.

Case	clinical diagnosis	Actual pH	PO_2	PCO_2	Factor VII	Fibrinogen	FDP
HA	breech presentation	7.01	11.4	65.7	14	96	1: x80
MI	preeclampsia	6.53	7.0	114.8	18	120	x160
EN	preeclampsia	7.09	18.5	84.8	20	90	x80
YO	preeclampsia	7.08	12.4	48.6	24	116	x40
Mean		6.92	12.3	78.5	19	105	x90
normal		7.27 ± 0.08	24.5 ± 3.1	45.0 ± 9.8	34.8 ± 8.8	210.08 ± 18.6	1: x10

Tab. IV. Thrombelastogram values in newborn infants (mean ± S.D)

Cases	r	r + k	ma
normal delivery (30)	10.4 ± 4.3	15.8 ± 3.2	63.5 ± 8.6
delayed delivery (23)	11.2 ± 3.2	16.4 ± 2.8	61.4 ± 5.8
preeclampsia (21)	10.6 ± 5.2	14.8 ± 1.9	62.6 ± 6.8
breech presentation (18)	9.8 ± 3.9	15.1 ± 2.6	60.8 ± 4.6
cord nuchal or prolapse (10)	11.4 ± 4.6	14.5 ± 3.2	61.6 ± 3.9
normal adult (20)	12.6 ± 3.2	18.1 ± 4.0	53.8 ± 3.6

Tab. V. The correlation between the value of ma (narrower than 25 mm, TEG), FDP and actual pH.

1. ma of TEG

	cases	ma under 25 mm	%	
pH ≤ 7.1	12	7	58.3%	
pH > 7.1	90	3	3.3%	P < 0.01

2. FDP

	cases	over 10 μg/mg	%	
pH ≤ 7.1	12	9	75.0%	
pH > 7.1	90	8	8.9%	P < 0.05
	102	17	17 %	

Of these 17 cases,

normal delivery	(2 out of 30 cases)	6.6%
delayed delivery	(1 out of 23 cases)	4.3%
preeclampsia	(3 out of 21 cases)	14.2%
breech presentation	(6 out of 18 cases)	33.3%
cord nuchal	(5 out of 10 cases)	50%

positive FDP (over 10 μg/mg) are seen.

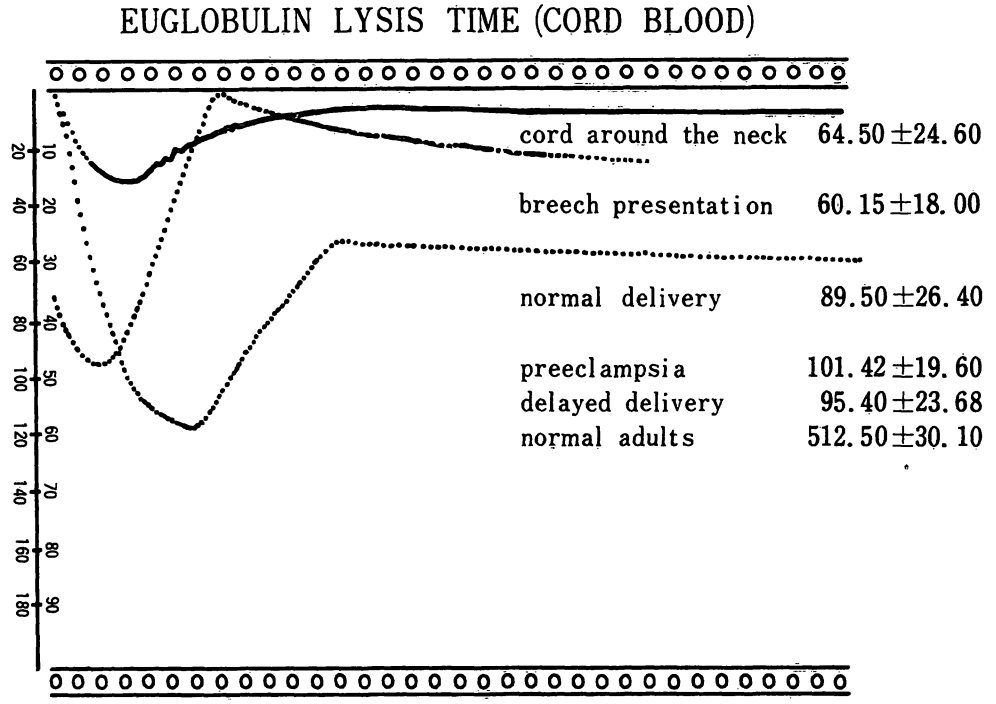

Fig. 3. Euglobulin lysis time detected by an automatic clot lysis time recorder (KANAMAN, Great Britain).

At the same time a remarkable decrease in the Normotest was observed, e.g. Normotest was under 25%, factor V under 20%, factor VII under 20%, thus indicating the coagulation deficiency. The results are shown in Tab. VII. In late pregnancy cases a highly intense blood coagulation disorder was seen, e.g. Normotest was 61% (14 cases out of 23), factor V 35% (8 cases out of 23), and factor VII 52% (12 cases out of 52).

Fibrinogen (2.2.6)

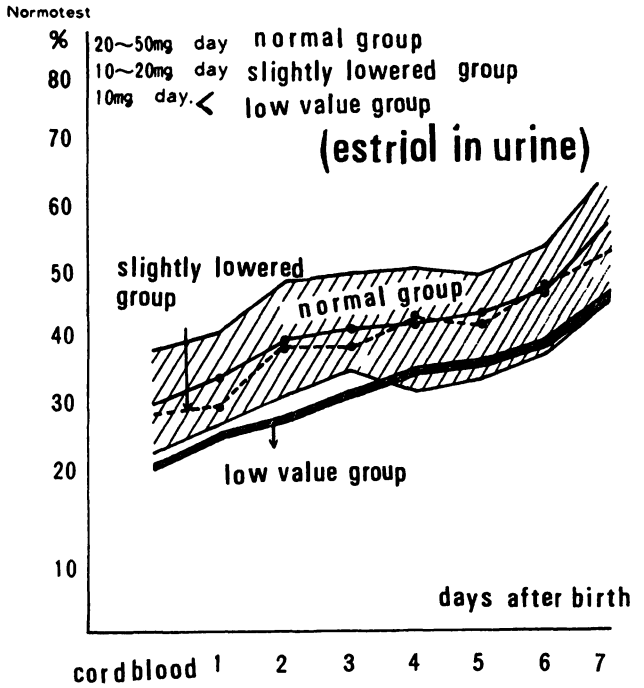

Fig. 4. Daily change of Hepaplastintest (Normotest).

Tab. VI. Factor V and factor VII in cord venous blood (mean ± S.D)

	Cases	
Factor V	normal delivery (30)	86.4 ± 2.80
	delayed delivery (23)	48.4 ± 8.60
	preeclampsia (21)	75.8 ± 4.18
	breech presentation (18)	78.6 ± 3.28
	cord nuchal and prolapse (10)	74.6 ± 2.96
Factor VII	normal delivery (30)	34.8 ± 8.76
	delayed delivery (23)	17.5 ± 8.41
	preeclampsia (21)	32.4 ± 10.60
	breech presentation (18)	31.6 ± 5.80
	cord nuchal and prolapse (10)	26.5 ± 4.65

Plasma fibrinogen levels are tested by the tyrosine method (RATNOFF–MENZIE). The results are as follows:

low group: (10 mg/day)	96.20 ± 26.4 mg/dl
slightly lower group: (10–20 mg/day)	178.46 ± 20.2 mg/dl
normal group: (20–50 mg/day)	216.09 ± 19.6 mg/dl

No positive correlation between the value of fibrinogen of cord-venous blood and the value of estriol (2.3) of the maternal urine was found, although the low group had an extremely low level of fibrinogen (Fig. 5).

4 Discussion

Since BELLER [3] pointed out the hypercoagulability of blood in newborns in 1957, the conventional concept of hypoprothrombinemia due to immature liver function in order to explain the malady is now insufficient and a broader viewpoint is required.

When the relationship of asphyxia of the newborn and the disorder of blood coagulation is studied, the first problematic point is the condition of delivery.

In newborn infants abnormal delivery conditions which may give rise to acidosis have a strong tendency to cause socalled disseminated intravascular coagulation.

In the delivery types presented in this article, prolapsed cord and breech presentation showed a high rate of fibrin split products complicated by a lowering of fibrinogen. This is clearly indicative of a high risk at delivery. In such cases slow circulation gives rise to hypercoagulability, but there is no problem as long as delivery is completed while the condition mentioned above is still in a preparatory state of intravascular coagulation; however, if there is a delay in delivery or when a high degree of anoxia appears, such changes may become irreversible. If the above changes occurring at the time of delivery are considered as an acute pattern, the changes in late pregnancy would be quite different.

Fibrinogen is lowered and, although the normotest shows low values, no rise in FDP is seen. The explanation for this may be as folows: Although no correlation is seen between the maternal urinary estriol and the fibrinogen volume in the cord blood of the group which showed under 10 mg/day estriol, 5 cases out of 6 showed under 100 mg/ml fibrinogen. This might represent an insufficiency of fibrinogen biosynthesis in the liver.

It is well understood that the significance of urinary estriol determination lies in the study of the fetus-placental system. The main mechanism is to determine whether androgens from the fetal suprarenal gland are aromatized when they arrive at the placenta and will be converted to estriol [14].

This course is well known as the neutral pathway, and it is known that the fetus uses its own liver to

Tab. VII. The percentage of the newborn infant who are suffering from blood coagulation disorders

1. Normotest, Factor V, Factor VII

		Cases	under 25%	%	P
Normotest	normal delivery	30	5	17	
	delayed delivery	23	14	61	$p < 0.01$
	preeclampsia	21	6	28	
	breech presentation	18	6	33	
	cord nuchal and prolapse	10	4	40	
Factor V		Cases	under 20%	%	P
	normal delivery	30	2	7	
	delayed delivery	23	8	35	$p < 0.05$
	preeclampsia	21	4	19	
	breech presentation	18	2	11	
	cord nuchal and prolapse	10	2	20	
Factor VII		Cases	under 20%	%	P
	normal delivery	30	6	20	
	delayed delivery	23	12	52	$p < 0.05$
	preeclampsia	21	5	24	
	breech presentation	18	5	28	
	cord nuchal and prolapse	10	3	30	

2. Fibrinogen

		Cases	under 150 mg	%	P
	normal delivery	30	2	7	
	delayed delivery	23	10	43	$p < 0.01$
	preeclampsia	21	6	28	
	breech presentation	18	8	44	$p < 0.01$
	cord nuchal and prolapse	10	4	40	$p < 0.05$

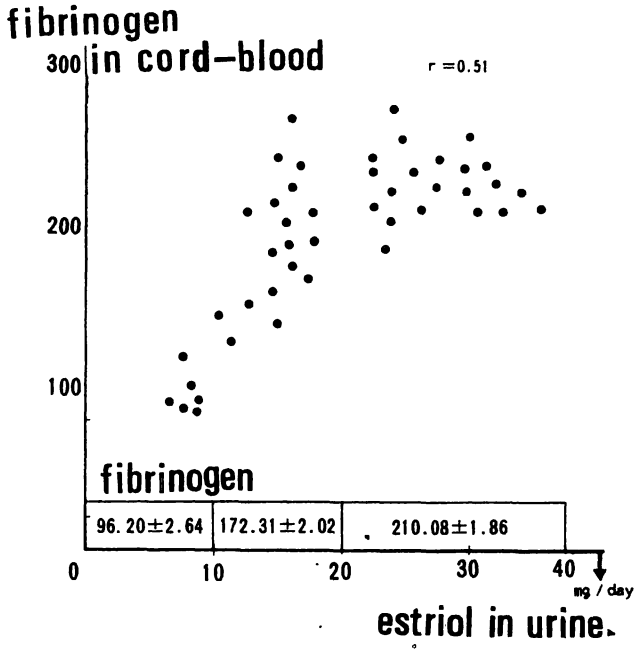

Fig. 5. The correlation between the value of fibrinogen (cord-blood) and the value of estriol in maternal urine.

change DHEA (dehydro-epiandrosterone) into 16α-hydroxyandrogen and to deliver it to the placenta, where it is followed by immediate production of estriol (Fig. 6).

This may be used indirectly as a criterion to determine the functional degree of the liver and in the late pregnancy group, the cause for low values of fibrinogen and normotest which indicate that the Vitamin K dependent factors may be low. This may be considered as follows: Whereas in the cord around the neck and breech presentation the change is drastic, in the late pregnancy group the pattern is comparatively chronic. The recent publication of HAUPT [7, 8, 9] depicts the outline of the pathway as shown in the diagram (Fig. 7). The ? portion is extremely complicated and complex, and it would be difficult to express this as a one unit component. This diagram explains the function of the fetus-placental system in late preg-

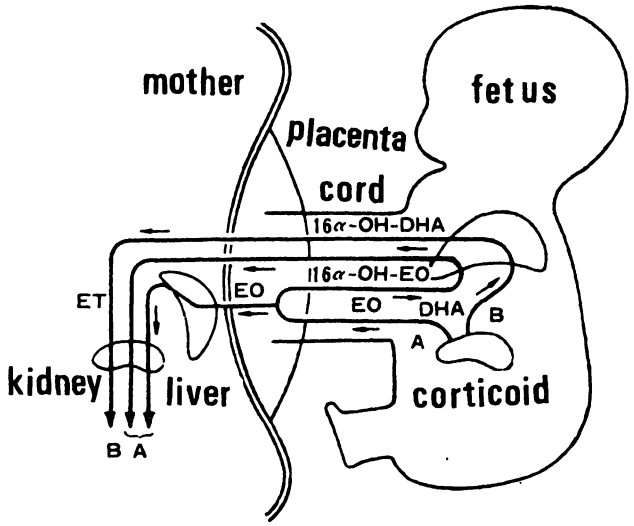

Fig. 6. The mechanism of estriol production.

nancy and at the same time shows the function of the liver. According to the diagram it may be possible to find at least an explanation. Furthermore, IWASAKI [10, 11, 12], YAMANAKA [23, 24, 25], when describing the so-called "Characteristics of Caesarian section syndrome" have stated that since the infant head is hardly subjected to pressure or crushing and since the operation is conducted prior to the onset of labor, the newborn infants delivered by this operation showed absolutely no rise in plasmin activity, and no decrease in fibrinogen.

Moreover, no fluctuations in FDP are seen, which indicates that these consecutive changes seen in the normal newborn may be considered as the crush syndrome of infants delivered under the pressure of the birth canal [13].

In fact, the onset of labor pains causes remarkable changes in the blood coagulation fibrinolytic system and at the same time certain changes in the fetal blood and feto-placental function. From this point of view, changes in various aspects of the neonatal period are important [20]. The first breath after birth causes lung expansion as well as activity of plasminogen-activator and becomes a primary factor for the acceleration of fibrinolysis. Morever, since the hemolytic effect after birth may well be related to this phenomenon, the starting point should naturally be sought for in the fetal period.

Acidosis at the time of birth becomes therefore a primary hemolytic factor.

It seems conceivable that an increase of FDP in asphyxia followed by DIC may have some influence on disseminated intravascular coagulation. Clarification of asphyxia in the newborn is therefore an important approach to be followed in the future.

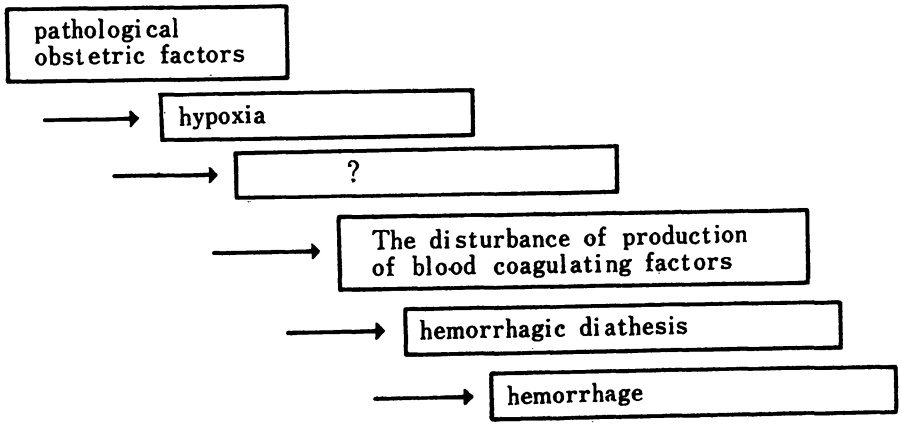

Fig. 7. The mechanism of early hemorrhage in newborn infants [4].

Summary

Hemorrhage in the newborn is an important disturbance in the adaptation to extra uterine life. A disturbance in the acid base balance initially indicates whether a neonate may survive. In order to clarify further the influences of prenatal and intrapartum problems on the coagulation system of the newborn, coagulation studies were carried out in 102 newborns including studies of fibrinolysis (fibrin split products (FDP) factor V, factor VII, fibrinogen

and euglobulin lysis time). These newborns were from normal deliveries as well as from delayed deliveries, breech presentations, nuclal cords and preeclampsia. The results were as follows:

1. **There is a distinct correlation between the actual pH (less than 7.10) and the occurrance of fibrin-split products.**
2. In late deliveries and cases of preeclampsia with decreased maternal estriol secretion there was a statistically significant difference in the levels of fibrinogen and Vitamin K-dependent coagulation factors when compared to controls. Thus, it is presumed that the placental dysfunction inhibits synthesis of coagulation factors as does liver immaturity. However, a typical consumption coagulopathy was not observed in these patients. In breech presentations and cord complications an increased FDP were seen. Thus, various abnormal deliveries may cause intravascular coagulation.
3. In breech presentation and cord complications the FDP were elevated.

Keywords: Coagulation, fibrinolysis.

Zusammenfassung

Blutgerinnung und Fibrinolyse beim Neugeborenen.
I. Aus geburtshilflicher Sicht

Blutungen bei Neugeborenen stellen unter Berücksichtigung der Anpassung an das extrauterine Leben eine bedeutende Störung dar.

Ein Ungleichgewicht des Säure-Alkali-Verhältnisses zeigt außerdem an, ob ein Neugeborenes lebensfähig ist.

Um diese Einwirkung pränataler Probleme beziehungsweise des Geburtsverlaufes auf das Gerinnungssystem des Neugeborenen deutlich zu machen, wurde an 102 Neugeborenen das Verhalten der Blutgerinnung und der Fibrinolyse, an mehreren hämostaseologischen Parametern (FDP, Faktor V, Faktor VII, Fibrinogen und Euglobulinlysis Zeit) untersucht.

Die Neugeborenen stammten von normalen Geburten, sowie Geburten mit verzögertem Verlauf, Beckenendlagen, Nabelschnurumschlingungen und Gestose. Folgende Ergebnisse lassen sich darstellen.

1. **Es gibt deutliche Beziehungen zwischen dem aktuellen pH-Wert (unter 7.1) und der Häufigkeit des Auftretens von Fibrin-Spalt-Produkten (FDP).**
2. Bei Übertragungen und Gestose-Fällen wurden zunächst zur Beurteilung einer bestehenden plazentaren Dysfunktion Östriol im mütterlichen Urin bestimmt.
   Bei niedrigem mütterlichen Östriol fand sich in den Fibrinogenwerten wie in Vitamin K abhängigen Faktoren eine statistisch signifikante Unterscheidung zur Kontrollgruppe.
   Es ist daher anzunehmen, daß die plazentare Dysfunktion damit eine störende Einwirkung auf die Synthese der Gerinnungsfaktoren hat, ebenso wie eine unreife Leber, obwohl eine typische Verbrauchskoagulopathie bei diesen Patienten nicht beobachtet werden konnte.
3. Bei Beckenendlagen und Nabelschnurumschlingungen konnte eine Erhöhung der FDP nachgewiesen werden.

   Unter dem Aspekt der Blutgerinnung können deshalb unterschiedliche Geburtsverläufe eine intravasale Gerinnung hervorrufen.

Schlüsselwörter: Blutgerinnung, Fibrinolyse.

Résumé

Coagulation sanguine et fibrinolyse du nouveau-né - Facteurs périnataux –
I. Coagulation sanguine et fibrinolyse du nouveau-né – Facteurs obstétriques –

Compte tenu du processus d'adaptation à la vie extra-utérine, les hémorragies témoginent de graves perturbations chez les nouveaux-nés.

Un déséquilibre du rapport acide-alcali sert également d'indice sur la viabilité d'un nouveau-né.

Afin de préciser l'influence des problèmes prénataux ou de l'accouchement sur le système de coagulation du nouveau-né, nous avons examiné chez 102 nouveaux-nés la courbe de coagulation sanguine et de fibrinolyse à l'aide de plusieurs paramètres hémostaséologiques (FDP, Facteur V, facteur VII, fibrinogène et temps d'euglobulinelyse).

Les sujets d'examen sont nés à la suite d'accouchement retardé, de position du siège, de circulaires du cordon ou de rpééclampsie. Les résultats obtenus peuvent se résumer comme suit:

1. **Il existe des rapports très nets entre la valeur actuelle de pH (inférieure à 7.1) et la fréquence de l'apparition de produits de fission de fibrine (FDP).**
2. Dans les cas d'accouchement postmaturé et de prééclampsie, nous avons procédé à un dosage d'oestriol dans l'urine maternelle afin d'établir si nous nous trouvions en présence d'une disfonction placentaire.

   Tant pour les valeurs de fibrinogène que pour les facteurs dépendant de la vitamine K, nous avons trouvé une différence statistiquement significative entre le groupe de contrôle et celui où avaient été enregistrés des taux peu élevés d'oestriol maternal.

   Il est donc à supposer que la disfonction placentaire a un effet perturbateur sur la synthèse des facteurs de coagulation, comme un foie non mature, bien que

nous n'ayions pu observer de coagulopathie de consommation typique chez ces patients.
3. Dans les cas de position du siège et de circulaires du cordon, nous avons pu observer une hausse de FDP.

En ce qui concerne la coagulation sanguine, on constate qu'une coagulation intravasale peut se produire en corrélation avec le déroulement de l'accouchement.

Mots-clés: Coagulation sanguine, fibrinolyse.

Bibliography see part II.

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